DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 26 1998

TRANSMITTED VIA FACSIMILE

Duane Burnham
CEO
Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, IL 60064-3500

RE: NDA #20-593
Depacon (valproate sodium) Injection
MACMIS #5616

WARNING LETTER

Dear Mr. Burnham:

This Warning Letter concerns Abbott Laboratories' ("Abbott") promotional materials and activities for the marketing of Depacon (valproate sodium) Injection. These materials were reviewed by the Division of Drug Marketing, Advertising, and Communications ("DDMAC") as part of its monitoring and surveillance program. We have concluded that Abbott has distributed materials that promote Depacon (valproate sodium) Injection for an unapproved use and thus are in violation of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 355(a), 352(a), 331(a), 331(d), and applicable regulations.[1] We are particularly concerned because we believe that the dissemination of these promotional materials raise significant safety issues regarding emergency treatment of a serious medical condition.

Despite the absence of a status epilepticus claim, Abbott's sales representatives have disseminated reprints of two articles that discuss the use of Depacon Injection in the

[1] These promotional materials include two reprints entitled "Use of injectable valproic acid in status epilepticus: A pilot study." (Giroud *et al.* 1993. *Drug Invest.* 5(3): 154-159) and "Safety of intravenous valproate" (Devinsky *et al.* 1995. *Ann. Neurol.* 38: 670-674).

treatment of status epilepticus. Abbott acknowledged to FDA that copies of the articles were provided to some of its regional and district managers who in turn provided these reprints to some sales representatives. Finally, Abbott failed to submit these materials to FDA as required by 21 C.F.R. § 314.81(b)(3)(i).

Background

The INDICATIONS AND USAGE section of its approved product labeling states that:

> Depacon is indicated as an intravenous alternative in patients for whom oral administration of valproate products is temporarily not feasible in the following conditions:
>
> Depacon is indicated as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures. Depacon is also indicated for use as sole or adjunctive therapy in the treatment of patients with simple and complex absence seizures, and adjunctively in patients with multiple seizure types that include absence seizures.

(The approved product labeling also defines simple absence and complex absence.)

The approved product labeling for Depacon **does not** contain an indication for status epilepticus.

Moreover, under "Clinical Studies," the Depacon product labeling refers to the studies conducted with **oral divalproex sodium products (Depakote)**, none of which involved a patient population with status epilepticus. Rather, these clinical trials examined the effectiveness of Depakote in reducing the incidence of complex partial seizures that occur in isolation or in association with other seizure types. There is thus no reference in the labeling to studies that would support the use of Depacon in status epilepticus.

Promotion of an Unapproved Use - Status Epilepticus

In disseminating reprints of publications that discuss the use of Depacon in the treatment of status epilepticus, Abbott has promoted an unapproved use of Depacon. Moreover, the reprints disseminated by Abbott do not appear to represent the type of adequate and well-controlled studies that would support a claim that Depacon is safe

and effective for the treatment of status epilepticus. The Giroud *et al.* reprint[2] ("Giroud") describes an open-label pilot study with no control arm (active or otherwise). The study included three patients who had status epilepticus due to cranial trauma. However, the Warnings section of the approved product labeling for Depacon suggests that Depacon not be used in this patient population. Specifically, the labeling states that, "until further information is available, it seems prudent **not** to use DEPACON in patients with acute head trauma for the prophylaxis of post-traumatic seizures." (Emphasis added).

The Devinsky *et al.* reprint[3] ("Devinsky") describes a "safety" study for the intravenous use of valproate. The study protocol listed various exclusion criteria. Status epilepticus was added as a specific exclusion criterion in the study after 99 patients had been enrolled. Nonetheless, the authors concluded that Depacon was potentially useful in the treatment on status epilepticus.

Abbott has acknowledged that these reprints were provided to some regional managers, district managers, and sales representatives. However, these reprints were subsequently distributed, by Abbott representatives, to healthcare providers including hospital pharmacists.

DDMAC is very concerned about Abbott's promotion of Depacon for status epilepticus, because it raises significant safety issues for this patient population. Status epilepticus is a neurological emergency that has a significant mortality risk. This emergency condition requires the administration of medications that are both safe and effective. The goal of treatment is the rapid termination of clinical and electrical seizure activity. In the absence of substantial evidence of safety and effectiveness, Abbott's promotion of Depacon may place a vulnerable patient population at great risk.

Failure to submit promotional materials

Finally, it should be noted that all promotional labeling and advertising materials used in promotion must be submitted to FDA according to the post-marketing reporting requirements for labeling and advertising, 21 C.F.R. § 314.81(b)(3)(i). As noted, Abbott failed to submit the Devinsky and Giroud reprints to FDA.

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[2] "Use of injectable valproic acid in status epilepticus: A pilot study." (Giroud *et al.* 1993. *Drug Invest.* 5(3): 154-159).

[3] "Safety of intravenous valproate" (Devinsky *et al.* 1995. *Ann. Neurol.* 38: 670- 674).

Conclusion and Requested Actions

The reprints and promotional messages that Abbott has been using promote Depacon (valproate sodium) Injection for an unapproved use. These materials contain or suggest false or misleading messages about the safety and effectiveness of Depacon for use in status epilepticus. Accordingly, Abbott should propose an action plan, including the mailing and publication of a "Dear Healthcare Professional" letter to disseminate corrective messages about this issue to all healthcare providers, institutions, and organizations who received the violative information.

This corrective action plan should also include:

A. Immediately ceasing the use of these reprints, and the dissemination of any information, verbal or printed, that contains false or misleading information about the use of Depacon for status epilepticus.

B. A written statement of Abbott's intent to comply with "A" above.

C. A complete listing of all Abbott personnel who have received these reprints, including their geographic locations. Abbott should instruct such personnel about lawful promotional practices, and should verify that these employees have received and understood directions received from Abbott regarding the use of reprints that discuss off-label uses for Depacon.

The "Dear Healthcare Professional" letter and Abbott's action plan should be submitted to DDMAC for prior approval. After such approval, the letter should be disseminated by direct mail.

Abbott's response should be received no later than July 13, 1998. If Abbott has any questions or comments, please contact Dr. Lisa Stockbridge, Dr. Lesley R. Frank, Esq., or Norman A. Drezin, Esq. by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 5616 in addition to the NDA number.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

/S/

Minnie Baylor-Henry, R.Ph., JD
Director
Division of Drug Marketing,
Advertising, and Communications